

Headache (chronic tension-type)

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Anita Krishnan and Nicholas Silver

ABSTRACT

INTRODUCTION: Chronic tension-type headache (CTTH) is a disorder that evolves from episodic tension-type headache, with daily or very frequent episodes of headache lasting minutes to days. It affects 4.1% of the general population in the USA, and is more prevalent in women (up to 65% of cases). **METHODS AND OUTCOMES:** We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of drug treatments for chronic tension-type headache? What are the effects of non-drug treatments for chronic tension-type headache? We searched: Medline, Embase, The Cochrane Library, and other important databases up to March 2007 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). **RESULTS:** We found 50 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. **CONCLUSIONS:** In this systematic review, we present information relating to the effectiveness and safety of the following interventions: acupuncture; amitriptyline; analgesics; anticonvulsant drugs; benzodiazepines; botulinum toxin; chiropractic and osteopathic manipulations; cognitive behavioural therapy (CBT); Indian head massage; mirtazapine; relaxation and electromyographic biofeedback; selective serotonin reuptake inhibitor antidepressants (SSRIs); and tricyclic antidepressants (other than amitriptyline).

QUESTIONS

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INTERVENTIONS

DRUG TREATMENTS		Regular analgesics (e.g., paracetamol, codeine, NSAIDs)	
Beneficial		
Amitriptyline	3	NON-DRUG TREATMENTS	
Likely to be beneficial		Unknown effectiveness	
Noradrenergic and specific serotonergic antidepressants (mirtazapine)	6	CBT	24
Unknown effectiveness		Acupuncture	26
SSRI antidepressants	12	Indian head massage	30
Tricyclic antidepressants (other than amitriptyline)	4	Relaxation or electromyographic biofeedback	30
Anticonvulsant drugs (valproate, topiramate, or gabapentin) New	23	Likely to be ineffective or harmful	
Likely to be ineffective or harmful		Spinal manipulation (chiropractic and osteopathic treatment) New	33
Benzodiazepines	16	To be covered in future updates	
Botulinum toxin	16	Other pharmacological treatments	

Key points

- Chronic tension-type headache (CTTH) is a disorder that evolves from episodic tension-type headache, with daily or very frequent episodes, lasting minutes to days.
 - It affects 4.1% of the general population in the USA, and is more prevalent in women (up to 65% of cases).
- We found only limited evidence about the treatment of CTTH.
 - Regular **analgesics** may lead to chronic headache symptoms and reduce the effectiveness of prophylactic treatment.
 - Amitriptyline** and **mirtazapine** may be equally effective in reducing the duration and frequency of CTTH, although amitriptyline may be associated with a less favourable adverse-effect profile.
 - We don't know whether **tricyclic antidepressants other than amitriptyline** are effective in treating CTTH.
 - We found no evidence examining the effectiveness of **noradrenergic and specific serotonergic antidepressants**, other than mirtazapine, in CTTH.
 - We don't know whether **SSRIs** are effective in treating CTTH.

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We don't know whether **benzodiazepines** are effective in treating CTTH, and they are commonly associated with significant adverse effects.

We found no evidence examining the effectiveness of **anticonvulsants**, such as sodium valproate, topiramate, and gabapentin, in CTTH.

Botulinum toxin does not seem to be a useful treatment for CTTH. It may be associated with several adverse effects, including facial weakness, difficulty in swallowing, and disturbed local sensation.

- We don't know whether non-drug treatments, such as **CBT**, **relaxation** or **electromyographic biofeedback**, or **acupuncture**, are effective in treating CTTH.

We don't know whether **chiropractic and osteopathic manipulations** are effective in treating CTTH. These treatments have been associated with rare, but very serious, adverse effects; for example, arterial dissection causing stroke, other stroke syndromes, and cerebellar and spinal cord injuries.

DEFINITION	Chronic tension-type headache (CTTH) is a disorder that evolves from episodic tension-type headache, with daily or very frequent episodes of headache lasting minutes to days. ^[1] The 2004 International Headache Society criteria for CTTH are: headaches on 15 or more days a month (180 days/year) for at least 3 months; pain that is bilateral, pressing, or tightening in quality and non-pulsating, of mild or moderate intensity, which does not worsen with routine physical activity (such as walking or climbing stairs); presence of no more than one additional clinical feature (mild nausea, photophobia, or phonophobia); and without moderate/severe nausea or vomiting. ^[1] CTTH is generally regarded as a featureless headache. Not all experts agree that mild features more typically seen in migraine (photophobia, phonophobia, etc.) should be included in the operational definition of CTTH, and it is often difficult to distinguish mild migraine headache from tension-type headache. CTTH is to be distinguished from other causes of chronic daily headache that require different treatment strategies (e.g., new daily persistent headache, medication overuse headache, chronic migraine, hemicrania continua). Many people who develop chronic daily headache owing to chronic migraine or medication overuse also develop mild migrainous "background" headaches that might be mistaken for coincidental CTTH. It is therefore extremely important to take a full headache history to elicit the individual features of the headache and look for prodromal or accompanying features that might indicate an alternative diagnosis. In contrast to CTTH, episodic tension-type headache can last from 30 minutes to 7 days, and occurs on fewer than 180 days a year. The greatest obstacle to studying tension-type headache is the lack of any single proved specific or reliable, clinical, or biological defining characteristic of the disorder. Terms based on assumed mechanisms (muscle contraction headache or tension headache) are not operationally defined. Old studies that used these terms may have included people with many different types of headache.
INCIDENCE/ PREVALENCE	The prevalence of chronic daily headache from a survey of the general population in the USA was 4.1%. Half of sufferers met the International Headache Society criteria for CTTH. ^[2] In a survey of 2500 undergraduate students in the USA, the prevalence of CTTH was 2%. ^[3] The prevalence of CTTH was 2.5% in a Danish population-based survey of 975 individuals. ^[4] One community-based survey in Singapore (2096 people from the general population) found that the prevalence was 1.8% in women and 0.9% in men. ^[5]
AETIOLOGY/ RISK FACTORS	Tension-type headache is more prevalent in women (65% of cases in one survey). ^[6] Symptoms begin before the age of 10 years in 15% of people with CTTH. Prevalence declines with age. ^[7] There is a family history of some form of headache in 40% of people with CTTH, ^[8] although a twin study found that the risk of CTTH was similar for identical and non-identical twins. ^[9]
PROGNOSIS	The prevalence of CTTH declines with age. ^[7]
AIMS OF INTERVENTION	To reduce the frequency, severity, and duration of headache, with minimal adverse effects from treatment.
OUTCOMES	Symptom severity: headache frequency, intensity, and duration. Adverse effects of treatment.
METHODS	<i>Clinical Evidence</i> search and appraisal March 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to March 2007, Embase 1980 to March 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 1. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributors for additional assessment, using pre-determined criteria to identify

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relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded, unless blinding was impossible. We also carried out an observational harms search for all chiropractic and osteopathic treatments, including prospective and retrospective cohorts, case-control, and case series studies. In addition, we use a regular surveillance protocol to capture harms alerts from organisations, such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 39). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of drug treatments for chronic tension-type headache?

OPTION TRICYCLIC ANTIDEPRESSANTS (AMITRIPTYLINE)

- For GRADE evaluation of interventions for Headache (chronic tension-type), see table, p 39 .
- Amitriptyline may be more effective than placebo in reducing headache duration and frequency.
- Amitriptyline and mirtazapine may be equally effective in reducing the duration and frequency of CTTH, although amitriptyline may be associated with a less-favourable adverse effect profile.


Benefits and harms

Amitriptyline versus placebo:



We found one systematic review (search date 1994; 1 RCT ^[10] ^[11] and five subsequent RCTs ^[12] ^[13] ^[14] ^[15] ^[16] comparing amitriptyline versus placebo (dosage range 10–150 mg; treatment duration 4–32 weeks). All but one of the RCTs ^[14] found that amitriptyline significantly improved headache duration and frequency in people with moderate-to-severe, properly-defined chronic tension-type headache. Most of the recent RCTs were small, of short-term duration, and used different outcome measures.

Symptom severity




Amitriptyline compared with placebo Amitriptyline may be more effective at reducing headache duration and frequency in people with moderate-to-severe chronic tension-type headache ([low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache scores					
^[10] RCT 3-armed trial	90 people Diagnosed using Criteria of the Ad Hoc Committee, 1962 ^[2] The remaining arm compared amitriptyline 25 mg 4-week trial duration	Reduction in mean headache score , 1 week with amitriptyline 10 mg with placebo	P <0.001 Mild reduction in headache scores at week 1 with amitriptyline 10 mg		amitriptyline
^[10] RCT 3-armed trial	90 people Diagnosed using Criteria of the Ad Hoc Committee, 1962 ^[2]	Reduction in mean headache score , 2 and 4 weeks with amitriptyline 10 mg with placebo	No reduction in headache scores at weeks 2 or 4 with amitriptyline 10 mg		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arm compared amitriptyline 25 mg 4-week trial duration				
[10] RCT 3-armed trial	90 people Diagnosed using Criteria of the Ad Hoc Committee, 1962 [2] The other arm compared amitriptyline 10 mg 4-week trial duration	Reduction in mean headache score , 1, 2, and 4 weeks with amitriptyline 25 mg with placebo	No difference noted at 1, 2, or 4 weeks with 25 mg dose of amitriptyline		
[12] RCT Crossover design 3-armed trial	40 people Diagnosed using IHS criteria [1] 32-week trial duration The remaining arm compared citalopram 20 mg	Reduction in area under headache curve (AUC) , 32 weeks with amitriptyline 75 mg with placebo AUC was calculated as daily headache duration x headache intensity	P = 0.002 for amitriptyline v placebo Results in 34/40 people (85%) who completed the trial Significant result for combined outcome resulted primarily from significant reductions in duration of headache (P = 0.01), rather than headache intensity (P = 0.12)	○○○	amitriptyline
[14] RCT 5-armed trial	203 people Diagnosed using Criteria of the Ad Hoc Committee, 1962 [2] The remaining arms evaluated nortriptyline, stress management, and stress management plus antidepressant drugs 4-week trial duration	Clinically important improvement (50% or more reduction in headache scores) , 4 weeks 34/53 (64%) with amitriptyline 14/48 (29%) with placebo	RR 2.19 95% CI 1.35 to 3.57	●●○	amitriptyline
[14] RCT 5-armed trial	203 people Diagnosed using Criteria of the Ad Hoc Committee, 1962 [2] The remaining arms evaluated nortriptyline, stress management, and stress management plus antidepressant drugs 4-week trial duration	Headache index scores , 4 weeks with amitriptyline with placebo	WMD 0.92 95% CI 0.44 to 1.41	○○○	amitriptyline
Headache duration, frequency, or intensity					
[13] RCT	53 people Diagnosed using IHS criteria [1] 6-week trial duration	Reduction in mean daily headache duration , 6 weeks 3.2 hours/day with amitriptyline 75 mg 0.28 hours/day with placebo	P < 0.01	○○○	amitriptyline

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[16] RCT Crossover design	27 people Diagnosed using IHS criteria [1] 8-week trial duration	50% reduction in headache frequency or severity with amitriptyline 75 mg/day with placebo	P <0.001		amitriptyline
[15] RCT 3-armed trial	203 people Diagnosed using Criteria of the Ad Hoc Committee, 1962 [2] 16-week trial duration	50% or more reduction in headache frequency, duration, and intensity with amitriptyline 50–75 mg with amitriptyline-N-oxide 60–90 mg with placebo	Reported as not significant for both amitriptyline and amitriptyline-N-oxide v placebo		Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Dry mouth					
[13] RCT Diagnosed using IHS criteria [1] 6-week trial duration	53 people	Dry mouth 54% with amitriptyline 75 mg 17% with placebo	P <0.05		placebo
Drowsiness					
[13] RCT Diagnosed using IHS criteria [1] 6-week trial duration	53 people	Drowsiness 62% with amitriptyline 75 mg 27% with placebo	P <0.05		placebo
Weight gain					
[13] RCT	53 people	Weight gain 16% with amitriptyline 75 mg 0% with placebo	Reported as not significant P value not provided		Not significant

Amitriptyline versus SSRI antidepressants:

See option on serotonin reuptake inhibitors, p 12 .

Amitriptyline versus mirtazapine:

See option on noradrenergic and specific serotonergic antidepressants, p 6 .

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Amitriptyline versus spinal manipulation:

See option on spinal manipulation., p 33

Amitriptyline versus CBT plus relaxation:

See option on CBT, p 24 .

Further information on studies

^[12] Similar results for adverse effects have also been found in other studies for amitriptyline.

Comment:

OPTION NORADRENERGIC AND SPECIFIC SEROTONERGIC ANTIDEPRESSANTS

- For GRADE evaluation of interventions for Headache (chronic tension-type), [see table, p 39](#) .
- Mirtazapine and amitriptyline may be equally effective in reducing the duration and frequency of CTTH, although mirtazapine may be associated with a more-favourable adverse effect profile.
- We found no direct information from RCTs about noradrenergic and specific serotonergic anti-depressants other than mirtazapine in the treatment of people with chronic tension-type headache.

Benefits and harms

Mirtazapine versus placebo:

We found two RCTs. ^[17] ^[18] One RCT examined mirtazapine 30 mg/day, ^[17] the other RCT examined low-dose mirtazapine 4.5 mg/day. ^[18]

Symptom severity

Mirtazapine compared with placebo Mirtazapine (30 mg/day) (but not low-dose mirtazapine [4.5 mg/day]) may be more effective at reducing headache frequency, duration, and intensity at 8 weeks ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
^[17] RCT Crossover design	24 people IHS criteria ^[1]	Headache frequency (days with headache) , last 4 weeks of treatment 25.5 with mirtazapine 28 with placebo Total trial duration 18 weeks	P = 0.005 The RCT did not report results before crossover, so results should be interpreted with caution	○○○	mirtazapine
^[17] RCT Crossover design	24 people IHS criteria ^[1]	Headache duration (hours with headache) , last 4 weeks of treatment 210 with mirtazapine 288 with placebo Total trial duration 18 weeks	P = 0.03 The RCT did not report results before crossover, so results should be interpreted with caution	○○○	mirtazapine
^[17] RCT Crossover design	24 people IHS criteria ^[1]	Headache intensity: verbal rating scale (0–10) , last 4 weeks of treatment 4.2 with mirtazapine 4.3 with placebo	P = 0.03 The RCT did not report results before crossover, so results should be interpreted with caution	○○○	mirtazapine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Total trial duration 18 weeks			
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine plus ibuprofen, and ibuprofen alone IHS criteria ^[1]	Headache frequency (change from baseline in days with headache) , last 4 weeks of treatment 28–28 with mirtazapine 28–28 with placebo	Reported as not significant P value not reported	↔	Not significant
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine plus ibuprofen, and ibuprofen alone IHS criteria ^[1]	Headache duration (change from baseline in hours with headache) , last 4 weeks of treatment 408–290 with mirtazapine 371–334 with placebo	Reported as not significant P value not reported	↔	Not significant
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine plus ibuprofen, and ibuprofen alone IHS criteria ^[1]	Headache intensity (change from baseline in 11-point verbal rating scale, from 0 = headache free to 10 = worst headache imaginable) , last 4 weeks of treatment 4.5–4.1 with mirtazapine 5.0–4.4 with placebo	Reported as not significant P value not reported	↔	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[17] RCT Crossover design	24 people	Proportion of people reporting one or more adverse effect 24/24 (100%) with mirtazapine 18/24 (75%) with placebo Adverse effects included drowsiness, dizziness, weight gain, dry mouth, increased appetite, oedema in extremities, sleep disturbances, nausea, concentration difficulties, irritability, and various (not defined)	P = 0.39	↔	Not significant
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine plus ibuprofen, and ibuprofen alone	Proportion of people reporting one or more adverse effect 14/23 (61%) with mirtazapine 10/23 (43%) with placebo Adverse effects included drowsiness, weight gain, dry mouth, increased appetite, improved sleep, irritability, dyspepsia, feeling "zombie-like", and various (not defined)	Significance not assessed		

Mirtazapine versus ibuprofen:

We found one four-armed RCT, which examined low dose mirtazapine (4.5 mg/day). ^[18]

Symptom severity

Mirtazapine compared with ibuprofen We don't know how low-dose mirtazapine and ibuprofen compare at reducing headache frequency, duration, or intensity at 8 weeks ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine plus ibuprofen, and placebo IHS criteria [1]	Headache frequency (change from baseline in days with headache) , last 4 weeks of treatment 28–28 with mirtazapine 28–27 with ibuprofen	Reported as not significant P value not reported	↔	Not significant
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine plus ibuprofen, and placebo IHS criteria [1]	Headache duration (change from baseline in hours with headache) , last 4 weeks of treatment 408–290 with mirtazapine 248–231 with ibuprofen	Reported as not significant P value not reported	↔	Not significant
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine plus ibuprofen, and placebo IHS criteria [1]	Headache intensity (change from baseline in 11-point verbal rating scale, from 0 = headache-free to 10 = worst headache imaginable) , last 4 weeks of treatment 4.5–4.1 with mirtazapine 4.2–4.4 with ibuprofen	Reported as not significant P value not reported	↔	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine plus ibuprofen, and placebo IHS criteria [1]	Proportion of people reporting one or more adverse effect 14/23 (61%) with mirtazapine 11/24 (46%) with ibuprofen	Significance not assessed		

Mirtazapine plus ibuprofen versus placebo:

We found one four-armed RCT, which examined low-dose mirtazapine (4.5 mg/day). [18]

Symptom severity

Mirtazapine plus ibuprofen compared with placebo Low-dose mirtazapine plus ibuprofen may be no more effective at reducing headache frequency, duration, or intensity at 8 weeks ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine alone, and ibuprofen alone IHS criteria ^[1]	Headache frequency (change from baseline in days with headache) , last 4 weeks of treatment 27–27 with mirtazapine plus ibuprofen 28–28 with placebo	Reported as not significant P value not reported	↔	Not significant
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine alone, and ibuprofen alone IHS criteria ^[1]	Headache duration (change from baseline in hours with headache) , last 4 weeks of treatment 275–164 with mirtazapine plus ibuprofen 371–334 with placebo	Reported as not significant P value not reported	↔	Not significant
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine alone, and ibuprofen alone IHS criteria ^[1]	Headache intensity (change from baseline in 11-point verbal rating scale, from 0 = headache free to 10 = worst headache imaginable) , last 4 weeks of treatment 4.9–4.5 with mirtazapine plus ibuprofen 5.0–4.4 with placebo	Reported as not significant P value not reported	↔	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine alone, and ibuprofen alone IHS criteria ^[1]	Proportion of people reporting one or more adverse effect 15/23 (65%) with mirtazapine plus ibuprofen 10/23 (43%) with placebo	Significance not assessed		
Drowsiness					
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine alone, and ibuprofen alone IHS criteria	Drowsiness 12/23 (52%) with mirtazapine plus ibuprofen 5/23 (22%) with placebo	P <0.05	○○○	placebo
Weight gain					
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine alone, and ibuprofen alone IHS criteria ^[1]	Proportion of people reporting weight gain 6/23 (23%) with mirtazapine plus ibuprofen 1/23 (4%) with placebo	P <0.05	○○○	placebo

Mirtazapine plus ibuprofen versus mirtazapine alone:

We found one four-armed RCT, which examined low dose mirtazapine (4.5 mg/day).^[18]

Symptom severity

Mirtazapine plus ibuprofen compared with mirtazapine alone Low-dose mirtazapine plus ibuprofen may be no more effective at reducing headache frequency, duration, or intensity at 8 weeks (*very low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
^[18] RCT 4-armed trial	93 people The remaining arms evaluated ibuprofen alone, and placebo IHS criteria ^[1]	Headache frequency (change from baseline in days with headache) , last 4 weeks of treatment 27–27 with mirtazapine plus ibuprofen 28–28 with mirtazapine	Reported as not significant P value not reported	↔	Not significant
^[18] RCT 4-armed trial	93 people The remaining arms evaluated ibuprofen alone, and placebo IHS criteria ^[1]	Headache duration (change from baseline in hours with headache) , last 4 weeks of treatment 275–164 with mirtazapine plus ibuprofen 408–290 with mirtazapine	Reported as not significant P value not reported	↔	Not significant
^[18] RCT 4-armed trial	93 people The remaining arms evaluated ibuprofen alone, and placebo IHS criteria ^[1]	Headache intensity (change from baseline in 11-point verbal rating scale, from 0 = headache-free to 10 = worst headache imaginable) , last 4 weeks of treatment 4.9–4.5 with mirtazapine plus ibuprofen 4.5–4.1 with mirtazapine	Reported as not significant P value not reported	↔	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
^[18] RCT 4-armed trial	93 people The remaining arms evaluated ibuprofen alone, and placebo IHS criteria ^[1]	Proportion of people reporting one or more adverse effect 15/23 (65%) with mirtazapine plus ibuprofen 14/23 (61%) with mirtazapine	Significance not assessed		

Mirtazapine plus ibuprofen versus ibuprofen alone:

We found one four-armed RCT, which examined low-dose mirtazapine (4.5 mg/day).^[18]

Symptom severity

Mirtazapine plus ibuprofen compared with ibuprofen Low-dose mirtazapine plus ibuprofen may be no more effective at reducing headache frequency, duration, or intensity at 8 weeks ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine alone, and placebo. IHS criteria [1]	Headache frequency (change from baseline in days with headache) , last 4 weeks of treatment 27–27 with mirtazapine plus ibuprofen 28–27 with ibuprofen	Reported as not significant P value not reported	↔	Not significant
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine alone, and placebo IHS criteria [1]	Headache duration (change from baseline in hours with headache) , last 4 weeks of treatment 275–164 with mirtazapine plus ibuprofen 248–231 with ibuprofen	Reported as not significant P value not reported	↔	Not significant
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine alone, and placebo IHS criteria [1]	Headache intensity (change from baseline in 11-point verbal rating scale, from 0 = headache-free to 10 = worst headache imaginable) , last 4 weeks of treatment 4.9–4.5 with mirtazapine plus ibuprofen 4.2–4.4 with ibuprofen	Reported as not significant P value not reported	↔	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine alone, and placebo IHS criteria [1]	Proportion of people reporting one or more adverse effect 15/23 (65%) with mirtazapine plus ibuprofen 11/24 (46%) with ibuprofen	Significance not assessed		

Mirtazapine versus amitriptyline:

We found one RCT. [19]

Symptom severity

Mirtazapine compared with amitriptyline Mirtazapine and amitriptyline may be equally effective at 6 months at reducing headache frequency and severity ([low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
^[19] RCT	60 people IHS criteria ^[1] Duration of trial 6 months	Percentage improvement in VAS score (scale 0–10); subjective assessment of combined headache frequency and intensity 65% with mirtazapine 58% with amitriptyline	Reported as not significant P value not reported Both treatments significantly reduced headache frequency and severity from baseline	↔	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
^[19] RCT	60 people IHS criteria ^[1]	Overall adverse effects with mirtazapine with amitriptyline Absolute results reported graphically Adverse effects, particularly dry mouth and drowsiness, were frequently reported	Reported as significantly less common with mirtazapine than amitriptyline P <0.001	○○○	mirtazapine

Further information on studies

Comment: The four-armed RCT ^[18] is also reported in the option on [analgesics](#), p 21 .

OPTION SEROTONIN REUPTAKE INHIBITORS

- For GRADE evaluation of interventions for Headache (chronic tension-type), [see table](#), p 39 .
- We don't know whether SSRIs are effective in treating CTTH.

Benefits and harms

SSRI antidepressants versus placebo:

We found one systematic review (search date 2005) ^[20] and one additional RCT. ^[21]

Symptom severity

SSRI antidepressants compared with placebo SSRI antidepressants may be no more effective at reducing headache symptoms ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
^[20] Systematic review	86 people 3 RCTs in this analysis	Index headache score with SSRIs (fluoxetine and sertraline)	SMD −0.14 95% CI −0.57 to +0.30	↔	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with placebo			
[12] RCT Crossover design 3-armed trial	40 people In review [20] Diagnosed using IHS criteria [1] The third-arm received amitriptyline	Headache duration (hours/day) with citalopram with placebo	WMD -0.07 95% CI -2.69 to +2.55 WMD calculated by systematic review; 34 people who completed the trial in this analysis	↔	Not significant
[12] RCT Crossover design 3-armed trial	34 people In review [20] Diagnosed using IHS criteria [1] The third arm received amitriptyline	Headache frequency (number of headache days) with citalopram with placebo	WMD -0.20 95% CI -3.94 to +3.54 WMD calculated by systematic review; 34 people who completed the trial in this analysis	↔	Not significant
[12] RCT Crossover design 3-armed trial	34 people In review [20] Diagnosed using IHS criteria [1] The third-arm received amitriptyline	Headache severity with citalopram with placebo	WMD -0.30 95% CI -1.13 to +0.53 WMD calculated by systematic review; 34 people who completed the trial in this analysis	↔	Not significant
[21] RCT	50 people	Headache frequency or headache index (a combined measure of frequency, severity, and duration of pain) with sertraline with placebo Absolute results not reported	Reported as not significant P value not reported	↔	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] RCT	50 people	Nausea with sertraline with placebo Nausea was reported in 6 people taking sertraline and 4 taking placebo	Significance not assessed		

SSRI antidepressants versus tricyclic antidepressant (amitriptyline):

We found one systematic review (search date 2005). [20]

Symptom severity

SSRI antidepressants compared with amitriptyline We don't know how SSRI antidepressants and amitriptyline compare at reducing headache duration (*very low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[20] Systematic review	152 people 2 RCTs in this analysis	Number of days with headache/month with SSRIs (sertraline and citalopram) with amitriptyline	WMD +0.76 95% CI -2.05 to +3.57	↔	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[20] Systematic review	64 people Data from 1 RCT	Withdrawals from treatment because of adverse events 3/32 (9.4%) with fluvoxamine 7/32 (21.9%) with amitriptyline	OR 0.39 95% CI 0.10 to 1.50	↔	Not significant
[20] Systematic review	64 people Data from 1 RCT	Minor adverse effects , within 1 week of treatment 4/32 (12.5%) with fluvoxamine 5/32 (15.6%) with amitriptyline Adverse effects included drowsiness, dry mouth, nausea, and general weakness	OR 0.77 95% CI 0.19 to 3.18	↔	Not significant

Further information on studies

Comment: **SSRI antidepressants, harms:**
Harms associated with the use of SSRIs are well described (see option on SSRIs in the reviews on Depression in adults: drug and physical treatments and Depression in children and adolescents).

OPTION TRICYCLIC ANTIDEPRESSANTS (OTHER THAN AMITRIPTYLINE)

- For GRADE evaluation of interventions for Headache (chronic tension-type), [see table, p 39](#).
- We don't know whether tricyclic antidepressants other than amitriptyline are effective in treating CTTH.



Benefits and harms

Tricyclic antidepressants (other than amitriptyline) versus placebo:

We found two RCTs. [22] [23]

Symptom severity

Tricyclic antidepressants (other than amitriptyline) compared with placebo We don't know whether maprotiline, clomipramine, or mianserin are more effective at reducing headache symptoms ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[22] RCT Crossover design	30 people Diagnosed by IHS criteria; 14-week trial duration	Reduction in headache intensity (increase in headache-free day) with maprotiline 75 mg/day with placebo 18/30 (60%) people found maprotiline better than placebo; 7 found it as effective; 3 found placebo better than maprotiline; 2 had no effect from either	P <0.001		maprotiline
[23] RCT	114 people Diagnosed by criteria of the Ad Hoc Committee 1962 (80% consistent with IHS criteria); 6-week trial duration	Greater than 50% reduction in intensity, 6 weeks with mianserin 30–60 mg with clomipramine 75–150 mg with placebo	Reported as non-significant reduction in area under curve (AUC) pain scores (calculated by area under the curve from graphed results) between mianserin, clomipramine, and placebo		Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[22] RCT Crossover design	30 people Diagnosed by IHS criteria; 14-week trial duration	Adverse effects with maprotiline with placebo Maprotiline was associated with a higher incidence of adverse effects (most notably sedation, dry mouth, and weight gain), but the authors reported these to be mild			
[23] RCT	114 people Diagnosed by criteria of the Ad Hoc Committee 1962 (80% consistent with IHS criteria)	Adverse effects with mianserin with clomipramine with placebo One person withdrew due to severe leukopenia associated with fever and glandular swelling. Other adverse effects were classed 'not serious', but still caused withdrawals			

Tricyclic antidepressants (other than amitriptyline) versus CBT plus relaxation::
See option on CBT, p 24 .

Further information on studies

Comment:

OPTION BENZODIAZEPINES

- For GRADE evaluation of interventions for Headache (chronic tension-type), [see table, p 39](#).
- We don't know whether benzodiazepines are effective in treating CTTH; they are commonly associated with serious adverse effects, such as an increased risk of motor vehicle accidents, falls and fractures, fatal poisonings, depression, dependency, decline in functional status, cognitive decline, confusion, erratic behaviour, and amnesia.

Benefits and harms

Benzodiazepines versus placebo:

We found no systematic review or RCTs that met our inclusion criteria.

Further information on studies

^[24] The adverse effects of benzodiazepines include increased risk of motor vehicle accidents, falls and fractures, fatal poisonings, depression, dependency, decline in functional status, cognitive decline, confusion, erratic behaviour, and amnesia.

Comment:

We found two RCTs that did not meet our inclusion criteria; one was too small (16 people), and the other did not meet the at least 80% follow-up criteria. Both RCTs found modest short-term improvements in chronic tension-type headache with benzodiazepines (diazepam or alprazolam). ^[25]
^[26]

OPTION BOTULINUM TOXIN

- For GRADE evaluation of interventions for Headache (chronic tension-type), [see table, p 39](#).
- Botulinum toxin does not seem to be a useful treatment for CTTH. It may be associated with several adverse effects including facial weakness, difficulty in swallowing, and disturbed local sensation.

Benefits and harms

Botulinum toxin versus placebo:

We found one systematic review (search date 2004, ^[27] 4 RCTs, ^[28] ^[29] ^[30] ^[31] 285 people) and three subsequent RCTs. ^[32] ^[33] ^[34] The review did not perform a meta-analysis because of heterogeneity in treatment doses and injection sites among studies, so we have reported the included RCTs separately. Some of the RCTs included in the review may have been too small to detect a clinically important difference between botulinum and placebo.

Symptom severity

Botulinum toxin compared with placebo Botulinum toxin may be no more effective at improving the symptoms of chronic tension-type headache ([low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache intensity					
^[28] RCT	59 people In review ^[27]	Proportion of people with >25% pain relief , 8 weeks 54% with botulinum 38% with placebo	P >0.05	↔	Not significant


Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[29] RCT	21 people In review [27] 2 RCTs in this analysis	Pain on 10-point visual analogue scale [VAS] , change from baseline to 12 weeks about 6.0 to about 5.0 with botulinum toxin about 6.0 about 4.5 with placebo Absolute results reported graphically	Reported as not significant P value not reported The RCT also found no significant difference in headache intensity, duration, and frequency at 4 and 8 weeks	↔	Not significant
[31] RCT	41 people In review [27]	At least 25% improvement in headache scores 13/22 (59%) with botulinum toxin 2/15 (13%) with placebo	Statistical significance not reported		
[32] RCT	40 people	Reduction of headache intensity (VAS) , 12 weeks with botulinum toxin (maximum 100 U) with placebo (saline)	Mean difference –3.5 mm 95% CI –20 mm to +13 mm	↔	Not significant
[33] RCT 6-armed trial	300 people	Mean reduction in average usual headache severity (assessed using 11-point scale, where 0 = no pain and 10 = worst pain) , 60 days –0.1 with botulinum toxin type A 150 units (5 sites) –0.1 with botulinum toxin type A 100 units (5 sites) –0.2 with botulinum toxin 100 units (3 sites) plus placebo (2 sites) –0.2 with botulinum toxin 86 units (3 sites) plus placebo (2 sites) –0.2 with botulinum toxin type A, 50 units (5 sites) –0.1 with placebo (5 sites) The RCT compared different doses of botulinum toxin type A (total dose: 50, 100, or 150 U [intramuscular injection] distributed between 5 muscle sites) v botulinum toxin type (total dose: 86 or 100 U [intramuscular injection] distributed between 3 muscle sites) plus placebo injected in 2 muscle sites v placebo injected in 5 muscle sites	Reported as no significant difference for any dose of botulinum toxin v placebo P value not reported Results of this RCT should be interpreted with caution (see further information on studies)	↔	Not significant
[34] RCT	40 people with frontal tension-type headache	Reduction in average headache intensity (using a Likert-type intensity scale, where 1–3 = mild, 4–6 = moderate, 7–9 = severe, and 10 = most painful headache ever experienced) , from baseline to average 178 days follow-up 5.19 to 4.65 with botulinum toxin (50 U distributed between 10 sites on the forehead) 5.38 to 5.27 with placebo	Difference between groups after treatment –0.620 95% CI –0.773 to –0.467	○○○	botulinum toxin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache duration					
[32] RCT	40 people	Headache hours/day with botulinum toxin (maximum 100 U) with placebo (saline)	Mean difference –1.4% 95% CI –3.9% to +1.1%	↔	Not significant
[33] RCT 6-armed trial	300 people	Mean reduction from baseline in % of the day spent with headache , 60 days –6.8% with botulinum toxin type A 150 units (5 sites) –3.0% with botulinum toxin type A 100 units (5 sites) –6.5% with botulinum toxin 100 units (3 sites) plus placebo (2 sites) –4.0% with botulinum toxin 86 units (3 sites) plus placebo (2 sites) –5.0% with botulinum toxin type A 50 units (5 sites) –4.7% with placebo (5 injection sites) The RCT compared different doses of botulinum toxin type A (total dose: 50, 100, or 150 U [intramuscular injection] distributed between 5 muscle sites) v botulinum toxin type (total dose: 86 or 100 U [intramuscular injection] distributed between 3 muscle sites) plus placebo injected in 2 muscle sites v placebo injected in 5 muscle sites	Reported as no significant difference for any dose of botulinum toxin v placebo P value not reported Results of this RCT should be interpreted with caution (see further information on studies)	↔	Not significant
Headache frequency					
[30] RCT	112 people In review [27]	Headache days/week , baseline to 12 weeks 6.6 to 6.3 with follow-up with botulinum toxin 6.7 to 6.5 with follow-up with placebo	P >0.11	↔	Not significant
[32] RCT	40 people	Mean number of headache days , 12 weeks with botulinum toxin (maximum 100 U) with placebo (saline)	Mean difference –7% 95% CI –20% to +4%	↔	Not significant
[32] RCT	40 people	Days on which symptomatic treatment taken with botulinum toxin (maximum 100 U) with placebo (saline)	Mean difference –1.9% 95% CI –11% to +7%	↔	Not significant
[33] RCT 6-armed trial	300 people	Mean change in tension-type headache-free days per month , from baseline to 30–60 days post injection 4.5 with botulinum toxin type A, 150 units (5 sites)	For botulinum 150 units v placebo: P = 0.007 For all other doses v placebo: reported as not significant, P values not reported	↔	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		<p>with botulinum toxin type A, 100 units (5 sites)</p> <p>with botulinum toxin type A, 50 units (5 sites)</p> <p>with botulinum toxin, 86 units (3 sites) plus placebo (2 sites)</p> <p>with botulinum toxin, 100 units (3 sites) plus placebo (2 sites)</p> <p>2.8 with placebo (5 sites)</p> <p>The RCT compared different doses of botulinum toxin type A (total dose: 50, 100, or 150 U [intramuscular injection] distributed between 5 muscle sites) v botulinum toxin type (total dose: 86 or 100 U [intramuscular injection] distributed between 3 muscle sites) plus placebo injected in 2 muscle sites v placebo injected in 5 muscle sites</p> <p>For all other doses v placebo absolute results presented graphically</p>	Results of this RCT should be interpreted with caution (see further information on studies)		
[34] RCT	40 people with frontal tension-type headache	<p>Change in mean number of headache episodes per month, from baseline to average 178 days follow-up</p> <p>from 23.4 to 17.1 with botulinum toxin</p> <p>from 23.4 to 18.4 with placebo</p>	<p>Reported as not significant</p> <p>P value not reported</p>	↔	Not significant
Combination headache severity outcomes					
[30] RCT	112 people In review [27]	<p>Reduction in product of headache frequency and intensity (area under curve)</p> <p>8% with botulinum toxin</p> <p>4% with placebo</p>	P = 0.91	↔	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[28] RCT	59 people In review [27]	<p>Adverse effects</p> <p>with botulinum toxin</p> <p>with placebo</p> <p>Vertigo occurred in 2 people with botulinum v 1 person with placebo; injection site pain occurred in 3 people with botulinum v 1 person with placebo after 4 weeks. By 8 weeks, symptoms had resolved</p>			
[30] RCT	112 people In review [27]	<p>Adverse effects</p> <p>with botulinum toxin</p> <p>with</p>	The RCT reported adverse effects only in the botulinum group		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		7 people experienced transient weakness of the eyelids, neck, or both (associated with pain in 1 person). 1 participant reported transient neck pain, and 1 had temporomandibular joint pain			
[31] RCT	41 people In review [27]	Proportion of people with adverse effects with botulinum toxin with placebo Adverse effects included muscle cramps, influenza-like symptoms, and subjective feelings of weakness in the neck muscles	Significance not reported		
[32] RCT	40 people	Adverse effects with botulinum toxin with placebo 21 people reported adverse effects (8 people with botulinum toxin v 13 people with placebo); the main complaint was short-lasting pain at the injection site			
[33] RCT 6-armed trial	300 people	Proportion of people with adverse effects 27/47 (62%) with botulinum toxin type A 150 units (5 sites) 33/51 (65%) with botulinum toxin type A 100 units (5 sites) 33/52 (64%) with botulinum toxin 100 units (3 sites) plus placebo (2 sites) 28/51 (55%) with botulinum toxin 86 units (3 sites) plus placebo (2 sites) 25/49 (51%) with botulinum toxin type A 50 units (5 sites) 26/50 (52%) with placebo (5 sites) The authors of the trial sub-categorised adverse effects as "treatment-related", and reported an overall incidence of 32%. The most frequent adverse effects reported were toxin-related muscular weakness (7%) and neck pain (5%) The RCT compared different doses of botulinum toxin type A (total dose: 50, 100, or 150 U [intramuscular injection] distributed between 5 muscle sites) v botulinum toxin type (total dose: 86 or 100 U [intramuscular injection] distributed between 3 muscle sites) plus placebo injected in 2 muscle sites v placebo injected in 5 muscle sites	Reported as not significant for all botulinum groups combined v placebo P value not reported		Not significant
[34] RCT	40 people with frontal tension-type headache	Adverse effects with botulinum toxin with placebo			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The RCT reported that botulinum toxin injections were well tolerated; 3 people reported ptosis symptoms, although this was not confirmed by examination, and resolved by 30 days. No other adverse effects were reported			

No data from the following reference on this outcome. ^[29] ^[27]

Further information on studies

^[33] The people included in the study were described as having chronic tension-type headache (CTTH). However, they may not satisfy the definition of CTTH used in this review: 95/300 (32%) people reported having at least one migraine headache per month; 105/300 (35%) reported associated symptoms with some of their headaches (including sensitivity to light and sound, nausea, and vomiting); and 13/300 (4%) people had fewer than 15 headaches per month. A total of 261/300 (87%) people used analgesic medication and 98/300 (33%) people used prophylactic headache medication during the study. These medications included aspirin, ibuprofen, paracetamol, paracetamol plus codeine, NSAIDs, beta-blockers, antidepressants, and anticonvulsants. It was not clear which groups used which medications. Results of this RCT should therefore be interpreted with caution.

Comment: Botulinum toxin may be associated with facial weakness, difficulty swallowing, and disturbed local sensation.

In contrast to the findings from the RCTs included in the review, most open studies included were in favour of botulinum toxin. ^[27]

OPTION REGULAR ANALGESICS (E.G., PARACETAMOL, CODEINE, NSAIDS)

- For GRADE evaluation of interventions for Headache (chronic tension-type), [see table, p 39](#).
- Regular analgesics may lead to chronic headache symptoms and reduce the effectiveness of prophylactic treatment.
- Note:** The FDA issued a drug safety alert on the risk of rare but serious skin reactions with paracetamol (acetaminophen) (August 2013).

Benefits and harms

Regular analgesics versus placebo:

We found no systematic review, but found one four-armed RCT ^[18] comparing ibuprofen alone (400 mg/day), placebo, low-dose mirtazapine (4.5 mg/day) plus ibuprofen, and mirtazapine alone (see [noradrenergic and specific serotonergic antidepressants, p 6](#)).

Symptom severity

Regular analgesics compared with placebo Ibuprofen may be no more effective at reducing headache frequency and duration 8 weeks, but may be more effective at decreasing the intensity of chronic tension-type headache ([low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine plus ibuprofen, and mirtazapine alone IHS criteria [1]	Headache frequency (days with headache) , from baseline to last 4 weeks of treatment 28–27 with ibuprofen 28–28 with placebo	Reported as not significant P value not reported	↔	Not significant
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine plus ibuprofen, and mirtazapine alone IHS criteria [1]	Headache duration (hours with headache) , change from baseline to last 4 weeks of treatment 248–231 with ibuprofen 371–334 with placebo	Reported as not significant P value not reported	↔	Not significant
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine plus ibuprofen, and mirtazapine alone IHS criteria [1]	Headache intensity (11-point verbal rating scale, from 0 = headache-free to 10 = worst headache imaginable) , from baseline to last 4 weeks of treatment 4.2–4.4 with ibuprofen 5.0–4.4 with placebo	P = 0.03	○○○	placebo

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] RCT 4-armed trial	93 people The remaining arms evaluated mirtazapine plus ibuprofen, and mirtazapine alone IHS criteria [1]	Proportion of people reporting one or more adverse effect 11/24 (46%) with ibuprofen 10/23 (43%) with placebo Adverse effects reported included drowsiness, weight gain, dry mouth, increased appetite, improved sleep, irritability, dyspepsia, feeling "zombie-like", and various others, which were not defined	Significance not assessed		

Ibuprofen versus mirtazapine:

See option on noradrenergic and specific serotonergic antidepressants, p 6 .

Ibuprofen plus mirtazapine versus placebo:

See option on noradrenergic and specific serotonergic antidepressants, p 6 .

Headache (chronic tension-type)

Ibuprofen plus mirtazapine versus ibuprofen:

See option on noradrenergic and specific serotonergic antidepressants, p 6 .

Ibuprofen plus mirtazapine versus mirtazapine:

See option on noradrenergic and specific serotonergic antidepressants, p 6 .

Further information on studies

^[18] This RCT is also reported in the option on [noradrenergic and specific serotonergic antidepressants](#), p 6 .

Comment:

We found one non-systematic review, which identified 29 observational studies (2612 people), and found no evidence of benefit of common analgesia for chronic tension-type headache (CTTH). It found that sustained frequent use (2–3 times/week) of some common analgesics in people with episodic headache was associated with chronic headache and reduced effectiveness of prophylactic treatment. ^[35]

Clinical guide:

Observational studies are difficult to interpret. From a practical, clinical perspective, it seems likely that all types of analgesic, when used on a regular basis, are capable of transforming acute headaches into chronic headaches in predisposed people. This applies to simple analgesics, such as paracetamol and NSAIDs, as well as opiates and compound analgesics containing mixes of different acute-attack medications (often including caffeine). In general, many headache experts advise people to eliminate medication overuse, and stop using acute-attack medications before considering preventive treatment for CTTH, or other types of chronic daily headache. Where medication overuse is contributing to chronic daily headache, withdrawal may lead to temporary and short-lived worsening of the headache disorder followed by possible improvement. Caffeine also seems to provide acute relief for some types of headache, although regular use may contribute to perpetuating the headache into a chronic state. It may be helpful for some people to avoid caffeine when faced with chronic daily headaches, such as chronic migraine or CTTH.

OPTION	ANTICONVULSANT DRUGS (VALPROATE, TOPIRAMATE, OR GABAPENTIN)	New
<ul style="list-style-type: none"> For GRADE evaluation of interventions for Headache (chronic tension-type), see table, p 39 . We found no direct evidence from RCTs examining the effectiveness of anticonvulsants such as sodium valproate, topiramate, or gabapentin in people with chronic tension-type headache. 		

Benefits and harms

Anticonvulsant drugs (sodium valproate, topiramate, or gabapentin):

We found no systematic review or RCTs.

Further information on studies

Comment:

QUESTION What are the effects of non-drug treatments for chronic tension-type headache?

OPTION CBT

- For GRADE evaluation of interventions for Headache (chronic tension-type), [see table, p 39](#).
- We don't know whether CBT is effective in treating CTTH.


Benefits and harms

CBT versus no CBT:

We found one systematic review (search date 1994, 3 small RCTs, 55 people). ^[11]

Symptom severity

CBT compared with no CBT We don't know whether cognitive therapy is more effective at improving headache symptoms ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
^[11] Systematic review	55 people 3 RCTs in this analysis	Symptoms with cognitive therapy with control	The review pooled data on cognitive therapy and found significantly greater improvement compared with control treatments The RCTs in the review were small and had as few as 8 people in each group. Clear conclusions could not be drawn		cognitive therapy

Adverse effects


No data from the following reference on this outcome. ^[11]

CBT plus relaxation versus placebo:

We found one four-armed RCT comparing stress management (combination treatment involving instruction on stress management skills, relaxation, and cognitive coping), tricyclic antidepressants (amitriptyline 100 mg/day or nortriptyline 75 mg/day), combined stress management plus antidepressants, and placebo. ^[14]

Symptom severity

CBT plus relaxation compared with placebo Stress management including cognitive coping may be more effective at reducing headache index scores at 6 months ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
^[14] RCT 4-armed trial	203 adults The other arms evaluated tricyclic antidepressants plus stress management, and tricyclic antidepressants alone	Headache index score (mean of pain ratings: score 0–10 where 10 is most severe pain, recorded in a diary 4 times/day), 6 months with stress management with placebo Stress management included combination treatment involving instruction on stress management	WMD 0.79 95% CI 0.30 to 1.28		stress management

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		skills, relaxation, and cognitive coping			
[14] RCT 4-armed trial	203 adults The other arms evaluated tricyclic antidepressants plus stress management, and tricyclic antidepressants alone	Clinically important improvement (50% or more reduction in headache index score) 17/49 (35%) with stress management 14/48 (29%) with placebo Stress management included combination treatment involving instruction on stress management skills, relaxation, and cognitive coping	RR 1.19 95% CI 0.66 to 2.13	↔	Not significant

Adverse effects

No data from the following reference on this outcome. [14]

CBT plus relaxation versus tricyclic antidepressants (amitriptyline or nortriptyline):

We found one four-armed RCT comparing stress management (combination treatment involving instruction on stress management skills, relaxation, and cognitive coping); tricyclic antidepressants (amitriptyline 100 mg/day or nortriptyline 75 mg/day); combined stress management plus antidepressants; and placebo. [14]

Symptom severity

CBT plus relaxation compared with tricyclic antidepressants We don't know how stress management including cognitive coping and amitriptyline or nortriptyline compare at reducing headache index scores at 6 months, or frequency of clinically important improvements (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache scores					
[14] RCT 4-armed trial	203 adults The remaining arms evaluated tricyclic antidepressants plus stress management, and placebo	Headache index score , 6 months with stress management with tricyclic antidepressants Stress management included combination treatment involving instruction on stress management skills, relaxation, and cognitive coping; tricyclic antidepressants included amitriptyline or nortriptyline	WMD -0.13 95% CI -0.61 to +0.35	↔	Not significant
[14] RCT 4-armed trial	203 adults The remaining arms evaluated tricyclic antidepressants plus stress management, and placebo	Clinically important improvement (50% or more reduction in headache index score) 17/49 (35%) with stress management 20/53 (38%) with tricyclic antidepressants Stress management included combination treatment involving instruction on stress management skills, relaxation, and cognitive	RR 0.92 95% CI 0.55 to 1.54	↔	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		coping; tricyclic antidepressants included amitriptyline or nortriptyline			

Adverse effects

No data from the following reference on this outcome. ^[14]

CBT versus relaxation or electromyographic biofeedback (alone or combined):

We found one systematic review (search date 1994; 9 comparative studies). ^[11] The studies compared relaxation or electromyographic biofeedback (or both) versus either CBT alone (2 studies) or plus relaxation or electromyographic biofeedback (7 studies). ^[11] The review did not perform a meta-analysis, and results from individual studies were inconclusive. The RCTs in the review were small and had as few as five people in each group. ^[11]

Adverse effects

No data from the following reference on this outcome. ^[11]

Further information on studies

Comment: The RCT of stress management combining relaxation and cognitive coping is also reported in the options on [relaxation or electromyographic biofeedback](#), p 30 ; [tricyclic antidepressants \(other than amitriptyline\)](#), p 14 ; and [tricyclic antidepressants \(amitriptyline\)](#), p 3 . ^[14]

Clinical guide:

Although the RCT comparing stress management (cognitive coping and relaxation), tricyclic antidepressants, combined stress management plus antidepressants, and placebo found that the headache index score was reduced with stress management compared with placebo, it found no convincing reduction in the number of people who had a clinically important response. The evidence is too limited to define the role of CBT in the treatment of CTTH.

OPTION ACUPUNCTURE

- For GRADE evaluation of interventions for Headache (chronic tension-type), [see table](#), p 39 .
- We don't know whether acupuncture is effective in treating CTTH.

Benefits and harms

Acupuncture versus sham acupuncture/minimum acupuncture:

We found two systematic reviews ^[36] ^[37] and three subsequent RCTs. ^[38] ^[39] ^[40] The first systematic review (search date 1998, 6 RCTs, 182 people) found significant heterogeneity among studies, making it difficult to summarise the results. ^[36] The second systematic review (search date 1998, 4 RCTs [including 3 RCTs identified by the first review], ^[36] 91 people) found insufficient evidence comparing the effectiveness of acupuncture versus sham acupuncture. ^[37] The review did not perform a meta-analysis owing to the heterogeneity of the included studies.

Many of the RCTs were of poor quality. Some may have lacked power to detect a clinically important effect. We have reported the results of the first systematic review below. ^[36]

Symptom severity

Acupuncture compared with sham acupuncture/minimum acupuncture We don't know whether acupuncture is more effective at improving headache intensity, duration, and frequency ([low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
^[36] Systematic review	48 people 2 RCTs in this analysis	Response rates (greater than 33% index reduction) 17/24 (71%) with acupuncture 11/24 (46) with sham acupuncture	RR 1.49 95% CI 0.96 to 2.03 The meta-analysis may have lacked power to detect clinically important differences	↔	Not significant
^[38] RCT	68 people; 47 with chronic tension-type headache (CTTH), 21 with episodic headache 2 RCTs in this analysis	Mean headache frequency , immediately after treatment 13.1 days/month with acupuncture 16.6 days/month with sham (non-penetrative) acupuncture 2 treatments were given weekly over 5 weeks	Reported as not significant P value not reported	↔	Not significant
^[38] RCT	68 people; 47 with CTTH, 21 with episodic headache 2 RCTs in this analysis	Mean headache frequency , 5 months after the end of the treatment 16.7 days/month with acupuncture 17.2 days/month with sham acupuncture 2 treatments were given weekly over 5 weeks	Reported as not significant P value not reported	↔	Not significant
^[40] RCT 3-armed trial	270 people; 124 with CTTH, 146 with episodic tension-type headache The third-arm evaluated a waiting list control group	Headache frequency (change in days with headache) , from baseline 4 weeks before randomisation to weeks 9-12 after randomisation 17.5–9.9 with acupuncture 17.7–10.8 with minimal acupuncture (of distant non-acupuncture points) 195 people in analysis	Mean difference –0.6 95% CI –2.4 to +1.2 P = 0.51	↔	Not significant
^[40] RCT 3-armed trial	270 people; 124 with CTTH, 146 with episodic tension-type headache The third-arm evaluated a waiting list control group	Headache frequency (change in hours with headache) , from baseline to weeks 9-12 after randomisation 153–88 hours with acupuncture 167–111 hours with minimal acupuncture (of distant non-acupuncture points) 195 people in analysis	Mean difference –8 hours 95% CI –33 to +17 P = 0.51	↔	Not significant
^[40] RCT 3-armed trial	270 people; 124 with CTTH, 146 with episodic tension-type headache The third-arm evaluated a waiting list control group	Change in headache score (1 = mild, 2 = moderate, 3 = severe) , from baseline to weeks 9-12 after randomisation 29.9–15.8 with acupuncture 30.9–17.2 with minimal acupuncture (of distant non-acupuncture points)	Mean difference –0.8 95% CI –4.4 to +2.7 P = 0.64	↔	Not significant

Headache (chronic tension-type)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		195 people in analysis			
[39] RCT	50 people with CT-TH	Median headache severity (measured by VAS) , 1 month –5 with laser acupuncture –1 with placebo (machine set to 0 output power)	P <0.001	○○○	laser acupuncture
[39] RCT	50 people with CT-TH	Median headache severity (measured by VAS) , 2 months –3 with laser acupuncture 0 with placebo (machine set to 0 output power)	P <0.001	○○○	laser acupuncture
[39] RCT	50 people with CT-TH	Median headache severity (measured by VAS) , 3 months –2 with laser acupuncture 0 with placebo (machine set to 0 output power)	P <0.001	○○○	laser acupuncture
[39] RCT	50 people with CT-TH	Number of days a month with headache , 1 month –15 days/month with laser acupuncture –2 days/month with placebo (machine set to 0 output power)	P <0.001	○○○	laser acupuncture
[39] RCT	50 people with CT-TH	Number of days a month with headache , 2 months –10 days/month with laser acupuncture 0 days/month with placebo (machine set to 0 output power)	P <0.001	○○○	laser acupuncture
[39] RCT	50 people with CT-TH	Number of days a month with headache , 3 months –8 days/month with laser acupuncture 0 days/month with placebo (machine set to 0 output power)	P <0.001	○○○	laser acupuncture
[39] RCT	50 people with CT-TH	Headache duration , 1 month –6 hours with laser acupuncture –1 hours with placebo (machine set to 0 output power)	P <0.001	○○○	laser acupuncture
[39] RCT	50 people with CT-TH	Headache duration , 2 months –4 hours with laser acupuncture 0 hours with placebo (machine set to 0 output power)	P <0.001	○○○	laser acupuncture
[39] RCT	50 people with CT-TH	Headache duration , 3 months –4 hours with laser acupuncture 0 hours with placebo (machine set to 0 output power)	P <0.001	○○○	laser acupuncture

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[40]	270 people; 124 with CTTH, 146 with episodic tension-type headache The third-arm evaluated a waiting list control group	Proportion of people reporting at least 1 adverse effect 23/132 (17%) with acupuncture 11/63 (17%) with minimal acupuncture In total, there were 30 adverse effects with acupuncture, and 14 adverse effects with minimal acupuncture Adverse effects included triggering of headache or other pain, haematoma, and dizziness.	Significance not assessed See further information about studies.		




No data from the following reference on this outcome. [36] [37] [38] [39]

Acupuncture versus no acupuncture:

We found one three-armed RCT. [40]

Symptom severity

Acupuncture compared with no acupuncture Acupuncture seems more effective at improving headache intensity, duration, and frequency ([moderate-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[40] RCT 3-armed trial	270 people; 124 with CTTH, 146 with episodic tension-type headache The third-arm evaluated minimally penetrating acupuncture	Headache frequency (change in days with headache) , from baseline 4 weeks before randomisation to weeks 9-12 after randomisation 17.5–9.9 with acupuncture 17.3–16.3 with no intervention 207 people in analysis	Mean difference –5.8 95% CI –7.6 to –4.0 P <0.001		acupuncture
[40] RCT 3-armed trial	270 people; 124 with CTTH, 146 with episodic tension-type headache The third-arm evaluated minimally penetrating acupuncture	Headache duration (change in hours with headache) , from baseline to 9-12 weeks after randomisation 153–88 hours with acupuncture 169–164 hours with no intervention 207 people in analysis	Mean difference –48, 95% CI –72 to –23 P <0.001		acupuncture
[40] RCT 3-armed trial	270 people; 124 with CTTH, 146 with episodic tension-type headache The third-arm evaluated minimally penetrating acupuncture	Change in headache score (1 = mild, 2 = moderate, 3 = severe) , from baseline to 9-12 weeks after randomisation 29.9–15.8 with acupuncture 29.3–26.4 with no intervention 207 people in analysis	Mean difference –10.9 95% CI –14.3 to –7.4 P <0.001		acupuncture

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[40] RCT 3-armed trial	270 people; 124 with CTTH, 146 with episodic tension-type headache The third-arm evaluated minimally penetrating acupuncture	Proportion of people reporting at least 1 adverse effect with acupuncture with no treatment No information given on adverse effects with acupuncture v no treatment See adverse effects of acupuncture v sham acupuncture above See further information on studies			

Further information on studies

- [40] The RCT reported two serious adverse events requiring hospital stays within 24 weeks of randomisation in the acupuncture group, and one in the waiting list (no intervention) group, which were considered by the authors to be unrelated to the treatment.
- [38] The RCT also found no significant difference in pain intensity, as measured using a visual analogue scale (no further data provided).

Comment: None.

OPTION INDIAN HEAD MASSAGE

- For GRADE evaluation of interventions for Headache (chronic tension-type), [see table, p 39](#).
- We found no direct information from RCTs about the effects of Indian head massage in people with chronic tension-type headache.

Benefits and harms

Indian head massage versus no treatment:

We found no systematic review or RCTs.

Further information on studies

Comment:

OPTION RELAXATION OR ELECTROMYOGRAPHIC BIOFEEDBACK

- For GRADE evaluation of interventions for Headache (chronic tension-type), [see table, p 39](#).
- We don't know whether relaxation or electromyographic biofeedback are effective in treating CTTH.

Benefits and harms

Relaxation or electromyographic feedback versus no relaxation or electromyographic feedback or versus each other:

We found two systematic reviews (search date 1994; ^[11] search date not reported ^[41]). The reviews did not distinguish between RCTs and observational studies. Appraisal of the papers within the reviews identified 10 relevant RCTs. ^[42] ^[43] ^[44] ^[45] ^[46] ^[47] ^[48] ^[49] ^[50] ^[51] The RCTs were generally of low quality, and clear conclusions could not be drawn (see further information on studies).

Symptom severity

Relaxation or electromyographic feedback compared with no relaxation or electromyographic feedback or versus each other We don't know how relaxation or electromyographic biofeedback and no relaxation or electromyographic feedback compare or compared with each other at improving symptoms (*very low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
^[42] RCT	12 matched pairs In review ^[11] ^[41] Data from 1 RCT	Pain hours with functional relaxation with placebo relaxation	Functional relaxation reduced pain hours Results should be interpreted with caution (see further information on studies)		
^[43] RCT 4-armed trial	311 people with muscle contraction headaches In review ^[11] ^[41] Data from 1 RCT The remaining arms evaluated electrical therapy, and multimodal treatment The full RCT had 1015 adults with migraine or muscular contraction headache defined by the ICD (702/1015 [69%] people followed for 3 years; analysis not by intention-to-treat)	Frequency of headaches 1.5 hours/week with biofeedback (78 people) 14.7 hours/week with relaxation (78 people)	P < 0.05 Results should be interpreted with caution (see further information on studies)	○○○	biofeedback
^[44] RCT	39 students with tension headache In review ^[11] ^[41] Data from 1 RCT	Headache scores with EMG biofeedback with type 1 sham feedback with type 2 sham feedback with no treatment	All EMG groups significantly improved headache scores compared with no treatment, but no significant difference between EMG groups Results should be interpreted with caution (see further information on studies)		
^[45] RCT	66 people with tension headache for an average of 4 days/week over 4-week baseline In review ^[11] ^[41] Data from 1 RCT	Number of people achieving 50% reduction in headache severity with relaxation alone with relaxation plus cognitive therapy with pseudomeditation with headache monitoring	Reported as not significant for relaxation alone or relaxation plus cognitive therapy v either pseudomeditation or headache monitoring Results should be interpreted with caution (see further information on studies)	↔	Not significant
^[46] RCT	53 people with CT-TH In review ^[11] ^[41]	Headache scores with clinic-based relaxation training	Reported as no significant difference		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Data from 1 RCT	with home-based relaxation training	Results should be interpreted with caution (see further information on studies)		
[47] RCT	28 people with "muscle contraction headache" for an average of 11.5 years In review [11] [41] Data from 1 RCT	Proportion with at least 50% improvement in headache severity 7/13 (54%) with EMG biofeedback 1/10 (10%) with alternative treatments	Reported as significant Results should be interpreted with caution (see further information on studies)	○○○	EMG biofeedback
[48] RCT	31 people with tension headache for at least 1 year In review [11] [41] Data from 1 RCT	At least 50% improvement in symptoms 6/13 (46%) with biofeedback 1/12 (8%) with relaxation	Reported as significant Results should be interpreted with caution (see further information on studies)	○○○	biofeedback
[49] RCT	69 people diagnosed on the Ad Hoc Committee on the Classification of Headache (1962) In review [11] [41] Data from 1 RCT	Symptom improvement with EMG biofeedback with relaxation	Reported as not significant Results should be interpreted with caution (see further information on studies)	↔	Not significant
[50] RCT	31 people with tension headache and 3 or more headaches/week for at least 1 year In review [11] [41] Data from 1 RCT	Headache outcomes with stress coping technique with biofeedback with waiting list control	Stress coping technique significantly improved headache outcomes compared with biofeedback and waiting list control Results should be interpreted with caution (see further information on studies)	○○○	Stress coping technique
[51] RCT	26 children with CTTH several times/week or daily In review [11] [41] Data from 1 RCT	Headache free days with relaxation training with no treatment	Reported as significant difference Results should be interpreted with caution (see further information on studies)	○○○	relaxation training

Adverse effects

No data from the following reference on this outcome. [11] [41]

Relaxation plus CBT versus placebo:

See option on CBT, p 24 .

Relaxation plus CBT versus tricyclic antidepressants:

See option on CBT, p 24 .

Headache (chronic tension-type)

Relaxation or electromyographic biofeedback versus CBT:

See option on CBT, p 24 .

Relaxation plus chiropractic and osteopathic treatment versus relaxation exercises alone:

See option on spinal manipulation (chiropractic and osteopathic treatment), p 33 .

Further information on studies

^[11] ^[44] The RCTs identified by the reviews were generally of low quality, and included a variety of different electromyographic biofeedback and relaxation techniques (alone or combined). Clear conclusions could not be drawn.

Comment: Relaxation and electromyographic biofeedback require additional trained staff and are both time consuming. The RCT of stress management combining relaxation and cognitive coping has also been reported in the options on CBT, p 24 , tricyclic antidepressants (other than amitriptyline), p 14 , and tricyclic antidepressants (amitriptyline), p 3 .^[14]

OPTION	SPINAL MANIPULATION (CHIROPRACTIC AND OSTEOPATHIC TREATMENT)	New
<ul style="list-style-type: none"> For GRADE evaluation of interventions for Headache (chronic tension-type), see table, p 39 . We don't know whether chiropractic and osteopathic manipulations are effective in treating CTTH. These treatments have been associated with rare, but very serious, adverse effects; for example, arterial dissection causing stroke, other stroke syndromes, and cerebellar and spinal cord injuries. 		

Benefits and harms

Chiropractic and osteopathic treatment versus no osteopathic treatment:

We found one systematic review (search date 2002^[52]) which identified a single RCT.^[53] We also found two systematic reviews which evaluated the frequency of adverse effects associated with spinal manipulation (see comment below).^[54] ^[55]

Symptom severity

Chiropractic and osteopathic treatment compared with no osteopathic treatment Osteopathic manipulation plus palpatory examination may reduce headache severity immediately after treatment in people with muscle tension-type headache (*very low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
^[53] RCT 3-armed trial	22 people with muscle-tension headache In review ^[52]	Reduction in mean headache severity (rated from 0, no symptoms, to 7, incapacitating pain) , immediately after treatment 1.9 with palpatory examination followed by osteopathic manipulation 0 with palpatory examination alone 0 with instruction to rest in supine position Absolute results reported graphically	Effect size 1.8 95% CI 0.4 to 3.2 Results should be interpreted with caution (see further information on studies)		palpatory examination followed by osteopathic manipulation

Adverse effects





No data from the following reference on this outcome. ^[53]

Chiropractic and osteopathic treatment versus tricyclic antidepressants (amitriptyline):

We found two systematic reviews (search date not reported; ^[56] 2002 ^[52]), which both identified the same single RCT. ^[57]

Symptom severity

Chiropractic and osteopathic treatment compared with tricyclic antidepressants (amitriptyline) Spinal manipulation may be less effective after 6 weeks at improving headache intensity, but we don't know how it and amitriptyline compare at improving headache frequency. Spinal manipulation may be more effective at improving headache frequency and intensity at 4 weeks after treatment discontinuation compared with amitriptyline (*very low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
^[57] RCT	150 people with tension-type headache In review ^[52] ^[56] 6-week trial duration	Headache intensity (mean daily headache intensity assessed on a 0–20 scale; sum of 4 pain score ratings per day, each on a scale of 0–5, where 0 = no pain, and 5 = extremely intense, incapacitating pain) , 6 weeks 4.3 with spinal manipulation 3.2 with amitriptyline See further information on studies	Difference between groups 1.1 95% CI 0.2 to 2.0 P = 0.01		amitriptyline
^[57] RCT	150 people with tension-type headache In review ^[52] ^[56] 6-week trial duration	Headache frequency (mean number of headache/week; headaches with pain score rating of 2 or more) , 6 weeks 8.6 with spinal manipulation 6.8 with amitriptyline	Difference between groups 1.9 95% CI –0.4 to +4.3 See further information on studies		Not significant
^[57] RCT	150 people with tension-type headache In review ^[52] ^[56] 6-week trial duration	Headache intensity (mean daily headache intensity assessed on a 0–20 scale; sum of 4 pain score ratings per day, each on a scale of 0–5, where 0 = no pain, and 5 = extremely intense, incapacitating pain) , at 10 weeks (4 weeks after treatment discontinuation) 3.8 with spinal manipulation 5.2 with amitriptyline	Difference between groups 1.9 95% CI 0.4 to 4.3 P = 0.003 See further information on studies		spinal manipulation
^[57] RCT Identified by two systematic reviews ^[52] ^[56] 6 week trial duration	150 people with tension-type headache	Headache frequency (mean number of headache/week; headaches with pain score rating of 2 or more) , at 10 weeks (4 weeks after treatment discontinuation) 7.6 with spinal manipulation 11.8 with amitriptyline	Difference between groups 4.2, 95% CI 1.9 to 6.5 P = 0.0004 See further information on studies		spinal manipulation

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[57] RCT	150 people with tension-type headache	Adverse effects with spinal manipulation with amitriptyline The RCT did not compare adverse effects between groups RCT reported 46/56 (82%) people in the amitriptyline group had adverse effects (including dry mouth, drowsiness, or weight gain) and 3/70 (4%) people with spinal manipulation had neck stiffness after the first treatment that disappeared after 2 weeks of treatment	Significance not assessed		

Chiropractic and osteopathic treatment plus relaxation versus relaxation exercises alone:

We found one RCT. [58]

Symptom severity

Chiropractic or osteopathic treatments plus relaxation compared with relaxation exercises alone Osteopathic manipulation plus relaxation may be more effective at improving headache frequency, but we don't know how it and relaxation exercises alone compare at improving headache severity at 6 to 7 weeks (*very low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[58] RCT	29 people with tension-type headache (including CTTH, episodic, and probable tension-type headache)	Mean headache-free days/week, 6 to 7 weeks 1.79 with osteopathic treatment plus progressive muscular relaxation exercises 0.21 with progressive muscular relaxation exercises alone See further information on studies	P = 0.016	○○○	osteopathic treatment plus progressive muscular relaxation exercises
[58] RCT	29 people with tension-type headache, including CTTH, episodic, and probable tension-type headache	Improvement in headache intensity (6-point scale ranging from 0 = no headache to 5 = incapacitating headache), from baseline 6 to 7 weeks 1.88 with osteopathic treatment plus progressive muscular relaxation exercises 0.66 with progressive muscular relaxation exercises alone See further information on studies	P = 0.075	↔	Not significant

Adverse effects

No data from the following reference on this outcome. [58]

Further information on studies

- [53] Each group had a single 10-minute session of the assigned treatment. Osteopathic manipulation involved soft tissue procedures (kneading, deep pressure, and stretching) over the entire axial skeleton and high-velocity, low-amplitude procedures. The RCT had a number of weaknesses: first, the older definition of muscle tension-type headache was used in this study, which may have differed from the definition of chronic tension-type headache (CTTH) used in this review; second, the method of randomization was not reported; and third, it only assessed the immediate effects after a single treatment, and as such, provides little information about the role of osteopathic manipulation in the management of chronic or recurrent headache.
- [57] People in the spinal manipulation group received two 20-minute sessions of spinal manipulation per week for 6 weeks using short-lever, low-amplitude, high-velocity thrust techniques. People in the amitriptyline group received 10 mg daily in the first week, 20 mg daily in the second week, and 30 mg daily for the next 4 weeks, with dose reduction (not specified) if adverse effects, such as drowsiness and dry mouth, were not tolerated.
- [58] Osteopathic treatment involved one treatment per week for 3 consecutive weeks focusing on the pelvis, cranium, cervical and upper thoracic spine, clavicles, and upper ribs. PMR exercises were carried out at home for 20 minutes once a day. Participants were provided with an audiotape and typed instructions on PMR exercises, telling them to maximally contract major muscle groups, moving from the feet up to the head, to experience the sensation of the contraction and then the subsequent relaxation.

Comment:

Harms of chiropractic and osteopathic treatment:

We found two systematic reviews, which identified observational studies of harms of spinal manipulation (search date 1997, 177 cases; [54] search date not reported [publication date 1996], more than 110 cases, and one case series). [55] The harms reported in both of these reviews related to the use of cervical spine manipulation in general, and not specifically for the treatment of CTTH. The first review found that the most frequently reported serious adverse effects included arterial dissection, causing stroke, other stroke syndromes, and cerebellar and spinal cord injuries. Manipulation with rotational thrust was implicated in 23% of injuries. [54] The second review found that the majority of reported cases involved vertebrobasilar accidents with consequences, such as brainstem and cerebellar infarction, Wallenberg's syndrome (obstruction of the posterior inferior cerebellar artery), and locked-in syndrome (occlusion of basilar artery), with other reported complications including spinal cord compression, vertebral fracture, tracheal rupture, diaphragm paralysis, internal carotid haematoma, and cardiac arrest. The review found that one case series reported no serious neurological complications during 1 year among 460 providers and about 150,000 cervical manipulations. The authors commented that it is difficult to estimate the frequency of complications because of the uncertainty of caseload and the number of cervical manipulations received over a specified period of time. However, they estimated the rate of complications to be one per million manipulations. [55]

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Anticonvulsant drugs New option added, for which we found no systematic review or RCTs. Categorised as Unknown effectiveness.

Spinal manipulation (chiropractic and osteopathic treatment) Two systematic reviews and one further RCT added to benefits and harms. [56] [52] [58] One RCT identified by one review found greater reduction in headache severity after treatment with palpatory examination plus osteopathic manipulation versus palpatory examination alone or versus instruction to rest in people with muscle tension-type headache. [53] One RCT identified by both reviews found a reduction in headache intensity with amitriptyline versus spinal manipulation after 6 weeks' treatment, but no significant reduction in headache frequency between groups. [57] However, there was a significant reduction in headache intensity and frequency with spinal manipulation compared with amitriptyline at 4 weeks after treatment

discontinuation.^[57] One further RCT found improved headache frequency with osteopathic treatment plus progressive muscular relaxation exercises versus progressive muscular relaxation exercises alone, but no significant difference between groups in headache intensity after 6–7 weeks' follow-up.^[58] Two systematic reviews of observational studies added to the harms section found reported cases of serious adverse effects, including arterial dissection causing stroke, other stroke syndromes, and cerebellar and spinal cord injuries with the use of spinal manipulation.^[54] ^[55] Categorisation as Likely to be ineffective or harmful.

Acupuncture One RCT added, comparing acupuncture versus minimum acupuncture versus no intervention.^[40] It found improvements in headache frequency, duration, and headache score (assessing headache intensity) with acupuncture compared with no intervention. It found no significant difference in any of these outcomes with acupuncture compared with minimum acupuncture.^[40] Categorisation unchanged (Unknown effectiveness).

Analgesics One RCT added found no significant difference in headache frequency and duration with ibuprofen alone, or plus low-dose mirtazapine, versus low-dose mirtazapine alone or placebo. It found an increase in headache intensity with ibuprofen alone compared with placebo.^[18] Categorisation unchanged (Likely to be ineffective or harmful).

Botulinum toxin Two RCTs added, comparing botulinum toxin versus placebo.^[33] ^[34] One RCT found an increase in headache-free days with botulinum toxin 150 U (but not with lower doses) versus placebo after 60 days. It found no significant difference in headache duration or average headache severity with botulinum toxin versus placebo after 60 days.^[33] The other RCT found a reduction in headache intensity, but no significant difference in headache frequency with botulinum toxin versus placebo at an average of 178 days' follow-up.^[34] Categorisation unchanged (Likely to be ineffective or harmful).

Noradrenergic and specific serotonergic antidepressants One RCT added found no significant difference in headache frequency, duration, or intensity with low-dose mirtazapine plus ibuprofen or mirtazapine alone versus ibuprofen alone or placebo.^[18] Categorisation changed (from Beneficial to Likely to be beneficial).

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Anita Krishnan

Specialist Registrar in Neurology
The Walton Centre for Neurology and Neurosurgery
Liverpool
UK

Nicholas Silver

Consultant Neurologist
The Walton Centre for Neurology and Neurosurgery
Liverpool
UK

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GRADE Evaluation of interventions for Headache (chronic tension-type).

Important out-comes	Symptom severity									
	Studies (Partici-pants)	Outcome	Comparison	Type of evi-dence	Quality	Consis-tency	Direct-ness	Effect size	GRADE	Comment
What are the effects of drug treatments for chronic tension-type headache?										
6 (271) ^{[10] [12] [13] [14] [15] [16]}	Symptom severity	Amitriptyline versus placebo	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of re-sults. Directness point deducted for heterogeneity in outcomes assessed	
2 (117) ^{[17] [18]}	Symptom severity	Mirtazapine versus placebo	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for low dose used	
1 (93) ^[18]	Symptom severity	Mirtazapine versus ibuprofen	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for low dose used	
1 (93) ^[18]	Symptom severity	Mirtazapine plus ibuprofen ver-sus placebo	4	0	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for low dose used	
1 (93) ^[18]	Symptom severity	Mirtazapine plus ibuprofen ver-sus mirtazapine alone	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for low dose used	
1 (93) ^[18]	Symptom severity	Mirtazapine plus ibuprofen ver-sus ibuprofen alone	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for low dose used	
1 (60) ^[19]	Symptom severity	Mirtazapine versus amitriptyline	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results	
5 (170) ^{[12] [20] [21]}	Symptom severity	SSRI antidepressants versus placebo	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for het-erogeneity in outcomes assessed	
2 (152) ^[20]	Symptom severity	SSRI antidepressants versus tri-cyclic antidepressant (amitripty-line)	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for nar-row range of comparators	
2 (144) ^{[22] [23]}	Symptom severity	Tricyclic antidepressants (other than amitriptyline) versus placebo	4	−2	−1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results	
7 (613) ^{[28] [29] [30] [31] [32] [33] [34]}	Symptom severity	Botulinum toxin versus placebo	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of re-sults. Directness point deducted for differences in out-comes assessed	
1 (93) ^[18]	Symptom severity	Regular analgesics versus placebo	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results	
What are the effects of non-drug treatments for chronic tension-type headache?										

Important outcomes	Studies (Participants)	Outcome	Comparison	Type of evidence	Symptom severity				GRADE	Comment
					Quality	Consistency	Directness	Effect size		
	3 (55) ^[11]	Symptom severity	CBT versus no CBT	4	−3	0	−1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and uncertainty about clinical significance of result. Directness point deducted for unclear control group
	1 (200) ^[14]	Symptom severity	CBT plus relaxation versus placebo	4	−2	−1	−1	0	Very low	Quality point deducted for sparse data and incomplete reporting of results. Consistency point deducted for lack of consistency in beneficial effects. Directness point deducted for multiple interventions used in comparison
	1 (200) ^[14]	Symptom severity	CBT plus relaxation versus tricyclic antidepressants (amitriptyline or nortriptyline)	4	−2	0	−1	0	Very low	Quality point deducted for sparse data and incomplete reporting of results. Directness point deducted for multiple interventions used in comparison
	9 (404) ^{[36] [38] [39] [40]}	Symptom severity	Acupuncture versus sham acupuncture/minimum acupuncture	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of episodic tension-type headache
	1 (270) ^[40]	Symptom severity	Acupuncture versus no acupuncture	4	0	0	−1	0	Moderate	Directness point deducted for inclusion of episodic tension-type headache
	10 (1015) ^{[42] [43] [44] [45] [46] [47] [48] [49] [50] [51]}	Symptom severity	Relaxation or electromyographic feedback versus no relaxation or electromyographic feedback or versus each other	4	−2	−1	−1	0	Very low	Quality points deducted for incomplete reporting of results and for poor-quality studies. Consistency point deducted for lack of consistent beneficial effects. Directness points deducted for heterogeneity in techniques used and for uncertainty about benefit
	1 (22) ^{[53] [52]}	Symptom severity	Chiropractic and osteopathic treatment versus no osteopathic treatment	4	−3	0	−1	0	Very low	Quality points deducted for incomplete reporting of results, sparse data, and short follow-up. Directness point deducted for uncertainty about diagnosis
	1 (150) ^[57]	Symptom severity	Chiropractic and osteopathic treatment versus tricyclic antidepressants (amitriptyline)	4	−2	−1	−1	0	Very low	Quality points deducted for incomplete reporting of results and sparse data. Consistency point deducted for lack of consistent beneficial effects. Directness point deducted for inclusion of people with different types of headache
	1 (29) ^[58]	Symptom severity	Chiropractic and osteopathic treatment plus relaxation versus relaxation exercises alone	4	−1	−1	−1	0	Very low	Quality point deducted for sparse data. Consistency point deducted for lack of consistent beneficial effects. Directness point deducted for inclusion of people with different types of headache

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.